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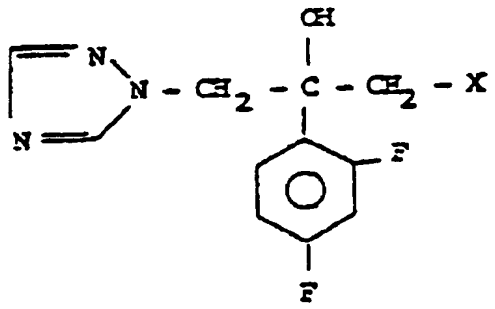
(54) **PROCEDE POUR LA PREPARATION DE TRIAZOLYLISOPROPANOLS**

(54) **PROCESS FOR THE PREPARATION OF TRIAZOLYL ISOPROPANOLS**



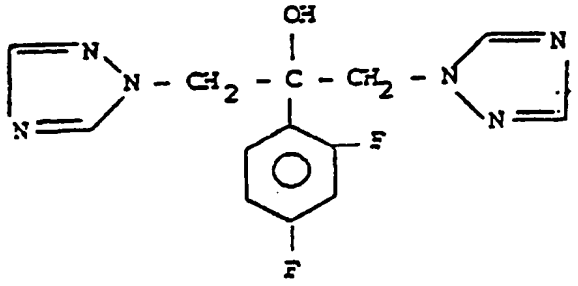
(II)

(57) Méthode améliorée d'obtention de fluconazole par réaction d'un intermédiaire halohydrinique avec un composé du type 4-amino-1,2,4-triazole de formule II (voir formule II) où X est le fluor, le chlore le brome ou l'iode, et par désamination à l'acide nitreux. Le fluconazole est un médicament antifongique efficace.

(57) An improved method for the preparation of fluconazole is described, by reacting an halohydrinic intermediate with 4-amino-1,2,4-triazole compound of formula II (see formula II) wherein X is fluorine, chlorine, bromine or iodine and subsequent deamination with nitrous acid. Fluconazole is useful as a antimycotic drug.

PROCESS FOR THE PREPARATION OF TRIAZOLYL ISOPROPANOLS

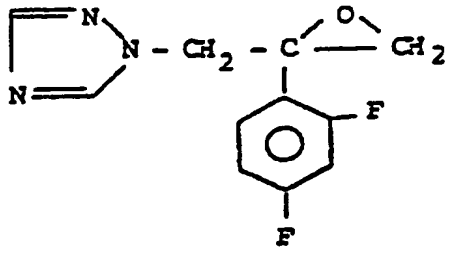
The present invention refers to a process for the preparation of 2-(2,4-difluorophenyl)-1,3-bis-(1H,1,2,4-triazol-1-yl)-2-propanol, of formula I



(I)

The compound I, also known with the name of fluconazole, is an antimycotic drug, disclosed in GB 2099818.

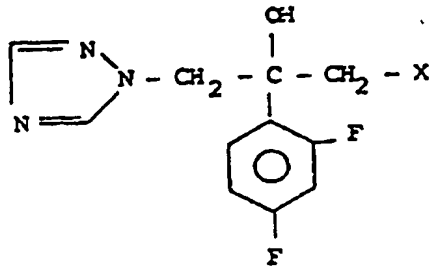
The known processes for the preparation of compounds I are characterized by the opening of an epoxidic intermediate of formula



with 1,2,4-triazole.

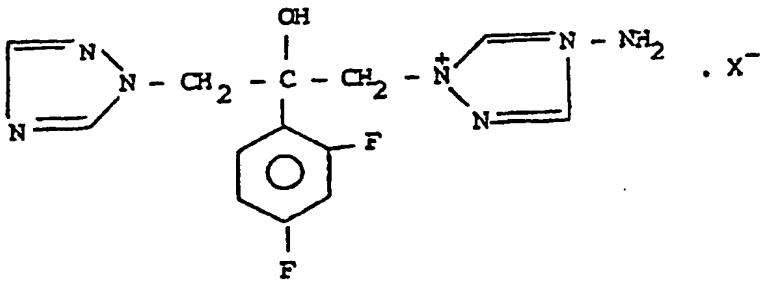
This reaction, however, is not selective, and yields the isomer 2-(2,4-difluorophenyl),1-(1H,1,2,4-triazol-1-yl),3-(4H,1,2,4-triazol-4-yl),2-propanol.

It has now been found that the compound I may be selectively obtained by reacting an halohydrin of formula II



(II)

wherein X is fluorine, chlorine, bromine or iodine with 4-amino-1,2,4-triazole to give the compound III



(III)

wherein X is above defined which, by reaction with nitrous acid in aqueous or alcoholic-aqueous medium, yields the compounds I with high yields and purity.

The compound III is new and it is a further object of the invention, as an intermediate.

The compound II can be easily prepared (a) from 2,4-difluorobenzene, magnesium bromide, by reaction with 1,3-dichloroacetone (Synthesis 1983,647) and then with 1H-1,2,4-triazole or (b) from α-chloro-2,4-difluoro-acetophenone by reaction with (1H-1,2,4-triazole-1) methyl magnesium chloride (Synthesis 1983,647) or (c) from 1-[2-(2,4-difluorophenyl)-2,3-epoxypropyl]-1H-1,2,4-triazole by reaction with hydrohalogen acids.

The reaction between compound II and 4-amino-1,2,4-triazole is preferably carried out in inert solvents such as C_1-C_5 alcohols, ketones, esters,

ethers.

The following examples further illustrate the invention.

EXAMPLE 1

2-(2,4-Difluorophenyl),1-(1H,1,2,4-triazol-1-yl),3-(4H,4-amino,1,2,4-triazonium-1-yl)2-propanol,bromide (III)

6.4 g of 2(2,4-difluorophenyl),1-bromo,3-(1H,1,2,4-triazol-1-yl)-2-propanol, are refluxed in 100 ml of isopropanol with 5.1 g of 4-amino-1,2,4-triazole for 8 hours. The reaction mixture is cooled to 0°C and the crystallized product is filtered. The crude wet product, so obtained, is refluxed with 50 ml of isopropanol, then refluxed, filtered and dried under vacuum at 40°C.

6.3 g (77.8%) of the title product are obtained.

EXAMPLE 2

2-(2,4-Difluorophenyl),1,3-bis-(1H,1,2,4-triazol-1-yl)-2-propanol (I)

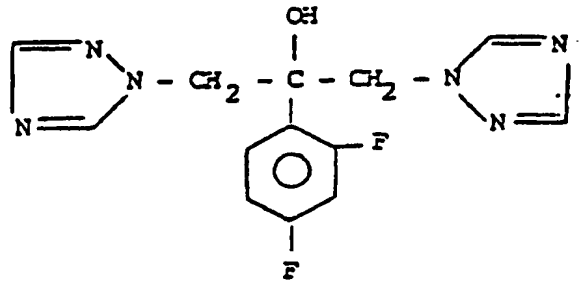
6.3 g of the product obtained in the Example 1 are dissolved in 60 ml of water and, cooling to 5°C, added with 1.8 g of concentrated hydrochloric acid. The solution is treated, at temperatures between 0 and 5°C, with a solution of 1.2 g of sodium nitrite in 6 ml of water. The reaction is continued at the same temperature for 30 minutes and then for at least 1 hour at 20°C. The so obtained solution is added with 500 mg of active charcoal and filtered. The so obtained clear solution is treated with concentrated ammonia up to pH 9 keeping the temperature at 20°C. When the product precipitation starts, the solution is cooled to 5°C for

at least 5 ml of water. The obtained crude product is crystallized from 25 ml of isopropanol. The filtered product is washed with 5 ml of cold isopropanol, dried at 40°C under vacuum.

4.1 g (85.4%) of the title product, having the same elemental analysis, mass, IR and NMR spectrum as a product sample obtained according to GB 2099818.

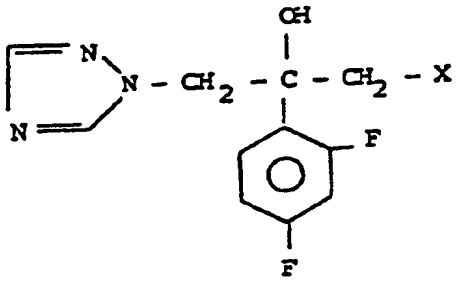
CLAIMS

1. A process for the preparation of the compound of formula I



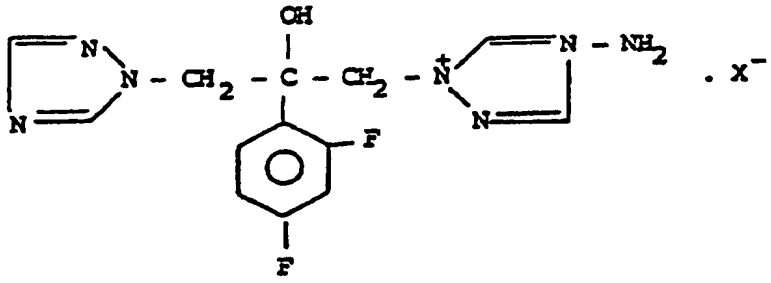
(I)

which comprises the reaction of a compound of formula II



(II)

wherein X is fluorine, chlorine, bromine or iodine with 4-amino-1,2,4-triazole to give the compound of formula III

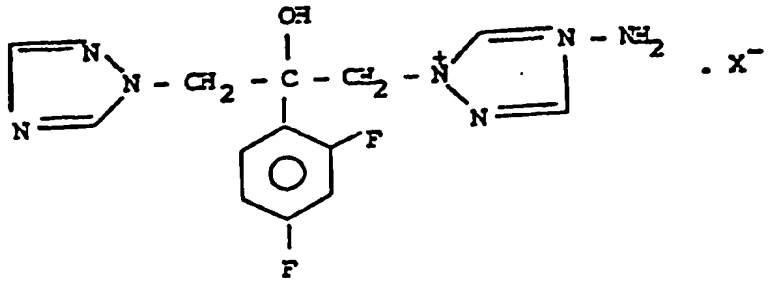


(III)

which is then reacted with nitrous acid.

2. A process according to claim 1 characterized in that a compound II wherein X⁻ is bromine is used.

3. Compound of formula III



(III)

wherein X is fluorine, chlorine, bromine or iodine.

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